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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,912	10/04/2004	Takahiro Ito	0020-5301PUS1	4489

2292 7590 02/11/2008
BIRCH STEWART KOLASCH & BIRCH
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EXAMINER	
LAU, JONATHAN S	
ART UNIT	**PAPER NUMBER**
1623	

NOTIFICATION DATE	DELIVERY MODE
02/11/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/509,912	ITO ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	4173	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 Dec 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 pg / 21Dec2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant application is the 371 national stage entry of PCT/JP03/04745, filed 15 Apr 2003; and claims benefit of foreign priority document JP 2002- 112864, filed 16 Apr 2002.

This Office Action is responsive to Applicant's amendment filed 21 Dec 2007, wherein claims 1-6 and 8-19 were amended and claim 7 was cancelled.

Claims 1-6 and 8-19 are pending.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 21 Dec 2007 was filed after the mailing date of the Office Action on 23 Aug 2007. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Objections Withdrawn

Applicant's amendment, filed 21 Dec 2007, with respect to the objections regarding the abstract of the disclosure has been fully considered and found to be persuasive to remove the objection as the amendment addresses the issues raised in this objection. Therefore this objection is **withdrawn**.

Applicant's amendment, filed 21 Dec 2007, with respect to the objections regarding informalities of claims 8 and 17 has been fully considered and found to be

persuasive to remove the objection as the amendment addresses the issues raised in this objection. Therefore this objection is **withdrawn**.

Applicant's amendment, filed 21 Dec 2007, with respect to the objections regarding the improper multiple dependency of claim 7 has been fully considered and found to be persuasive to remove the objection as the amendment addresses the issues raised in this objection. Therefore this objection is **withdrawn**.

Rejections Withdrawn

Applicant's amendment, filed 21 Dec 2007, with respect to the rejection of claims 1-6, 8, 10-13, 16, and 17 under 35 U.S.C. 102(b) as being anticipated by Harada et al. (Journal of Controlled Release, 2000, 69, p399-412, of record) have been fully considered and found to be persuasive to remove the rejection as the amendment addresses the issues raised in this rejections, as the limitations in the amended claims and the breadth and scope of the claims have been changed.

Therefore the previously stated rejection is **withdrawn**.

Applicant's amendment, filed 21 Dec 2007, with respect to the rejection of claims 1, 9, and 14-19 under 35 U.S.C. 103(a) as being unpatentable over Harada et al (Journal of Controlled Release, 2000, 69, p399-412, of record) in view of Wall et al. (US patent 5,340,817, issued 23 Aug 1994, of record) have been fully considered and found to be persuasive to remove the objection as the amendment addresses the issues raised in this rejections, as the limitations in the amended claims and the breadth and scope of the claims have been changed.

Therefore the previously stated rejection is **withdrawn**.

New or Modified Rejections

The following are new or modified rejections necessitated by Applicant's amendment filed 21 Dec 2007, wherein the limitations in pending claims 1-6 and 8-19 as amended have been changed, as claims 1 and 16 have been amended and claims 2-6 and 8-19 depend from amended claims. The limitations in the amended claims and the breadth and scope of the claims have been changed.

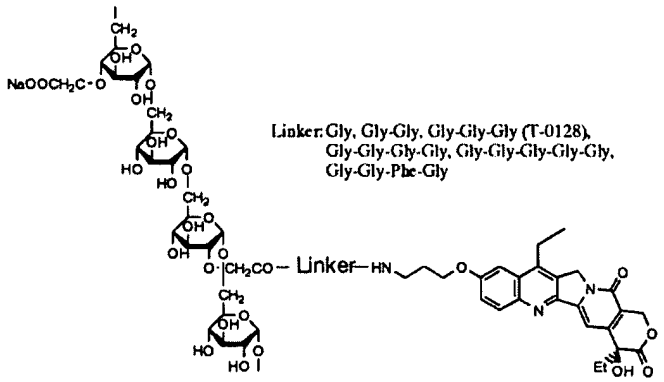
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 8, 10-13, 16, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Harada et al. (Journal of Controlled Release, 2000, 69, p399-412, of record).

Harada et al. discloses the compound T-0128, "a novel [camptothecin] analog (T-2513: 7-ethyl-10- aminopropyloxy-[camptothecin]) bound to carboxymethyl (CM) dextran through a Gly- Gly-Gly linker." See abstract lines 1-3. The compound T-0128

has the formula 

(Harada et al., page 401, figure 1). Harada et al. discloses a liquid preparation comprising the camptothecin analog T-0128 and an acetate buffer, reduced glutathione, EDTA, and Triton X-100, which are stabilizers or fillers, adjusted to pH 7 using acetate or phosphate buffers, optionally with $CaCl_2$, an alkaline earth metal chloride, added (page 402, right column, section 2.4. *In vitro evaluation of drug release*). The compound T-0128 addresses instant claims 1, 11-13 and 16. An acetate or acetic acid buffer addresses instant claims 2 and 17. The acetate or phosphate buffers are used at a concentration of 40 mM, which gives an ionic strength of less than 0.2, addressing instant claim 3. The liquid preparation adjusted to pH 7 addresses instant claims 1 and 4-6. The addition of stabilizers or fillers reduced glutathione, EDTA, and Triton X-100 addresses instant claim 8. The addition of $CaCl_2$, an alkaline earth metal chloride, addresses instant claim 10.

Reply to Applicant's amendment:

Applicant's amendment, filed 21 Dec 2007, with respect to the rejection of claims 1-6, 8, 10-13, 16, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by

Harada et al. (Journal of Controlled Release, 2000, 69, p399-412, of record) has been fully considered.

Amended claims 1 and 16 require a liquid preparation comprising 1 w/w% to 20 w/w% of a camptothecin derivative. However, Harada et al. discloses the compound T-0128 in saline at 0.5 mg/ml of T-2513, or 7-ethyl-10-aminopropyloxy-camptothecin (page 403, left column, lines 22-23). T-2153 has a molecular weight of approximately 485 g/mol. The compound T-0128 has a molecular weight of approximately 130,000 g/mol (page 402, lines 21-23). Therefore a liquid saline preparation that contains T-0128 at an amount equal to 0.5 mg/mL of T-2513 contains approximately 13.4 w/w% of the camptothecin derivative as calculated below:

(0.5 mg T-2153/mL H_2O * 130,000 g/mol T-0128 / 485 g/mol T-2153)

$\approx$ 134 mg T-0128/mL H_2O / 1000 mg/mL $H_2O \approx$ 134 mg T-0128 / 1000 mg H_2O

Therefore Harada et al. as relied upon in the Office Action mailed 23 Aug 2007 discloses a liquid preparation comprising approximately 13.4 w/w% of the camptothecin derivative, anticipating the range of instant claims 1 and 16 as amended.

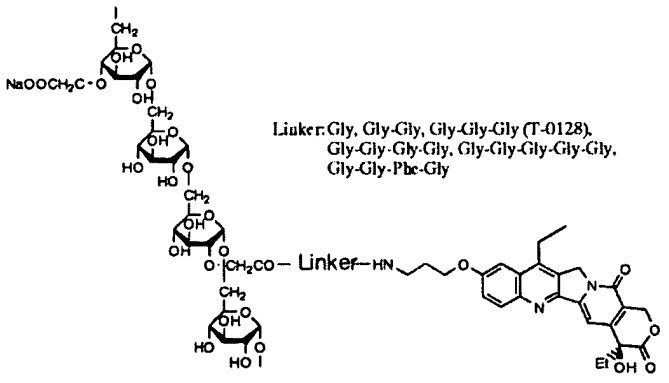
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 9, and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harada et al (Journal of Controlled Release, 2000, 69, p399-412, of record) in view of Wall et al. (US patent 5,340,817, issued 23 Aug 1994, of record).

Harada et al. discloses the compound T-0128, "a novel [camptothecin] analog (T-2513: 7-ethyl-10- aminopropyloxy-[camptothecin]) bound to carboxymethyl (CM) dextran through a Gly- Gly-Gly linker." See abstract lines 1-3. The compound T-0128 has the formula 

(Harada et al., page 401, figure 1). Harada et al. discloses a liquid preparation comprising the camptothecin analog T-0128 and an acetate buffer, reduced glutathione, EDTA, and Triton X-100,

which are stabilizers or fillers, adjusted to pH 7 using acetate or phosphate buffers, optionally with $CaCl_2$, an alkaline earth metal chloride, added (page 402, right column, section 2.4. *In vitro evaluation of drug release*).

Harada et al. does not disclose the use of alkali metal carbonates or alkali metal hydrogen carbonates as stabilizers or fillers such as lactose, sucrose, mannitol, dextran, maltose and trehalose (instant claim 9). Harada et al. does not disclose the lyophilized drug composition prepared by lyophilizing the liquid preparation (instant claim 14), or the liquid composition wherein the lyophilized drug composition is dissolved in an aqueous medium (instant claim 15). Harada et al. does not disclose a liquid preparation wherein the buffer is citric acid and sodium hydrogen phosphate (instant claim 18), optionally further containing sodium chloride (instant claim 19).

Wall et al. teaches a camptothecin analog that is a water-soluble derivative of camptothecin bound to an amino acid or peptide (column 8, lines 19-22) "incorporated into a solution or suspension. The solutions or suspensions may also include the following components: a sterile diluent such as water for injection, saline solution...; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ... disposable syringes ..." (column 13, lines 14-27). Wall et al. also teaches oral liquid compositions of a camptothecin analog, such as capsules, elixirs, suspensions, syrups, which generally include an inert diluent or an edible carrier and

incorporated with excipients (column 13, lines 29-36). Wall et al. teaches the specific excipients "such as starch or lactose, ... a sweetening agent such as sucrose" (column 13, lines 40 and 44). Wall et al. teaches the lyophilization of liquid preparations to provide the camptothecin derivatives (column 18, lines 30-31 and 52-53).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the liquid preparation of the camptothecin analog disclosed by Harada et al. with the pharmaceutical excipients in the pharmaceutical compositions of an amino acid- or peptide-bound camptothecin analog, the lyophilization of a liquid composition of a water-soluble amino acid-bound camptothecin analog, and the incorporation of the camptothecin analog prepared by lyophilization into a solution of sterile water for injection taught by Wall et al. One of ordinary skill in the art at the time of the invention would be motivated to combine the references because Wall et al. teaches the need for additional water-soluble camptothecin analogs (column 2 lines 2-5). One of ordinary skill in the art at the time of the invention would have a reasonable expectation of success in combining these references due to the similarity between the the camptothecin analog disclosed by Harada et al. and the amino acid-bound camptothecin analog taught by Wall et al.

Reply to Applicant's amendment:

Applicant's amendment, filed 21 Dec 2007, with respect to the rejection of claims 1, 9, and 14-19 under 35 U.S.C. 103(a) as being unpatentable over Harada et al (Journal of Controlled Release, 2000, 69, p399-412, of record) in view of Wall et al. (US patent 5,340,817, issued 23 Aug 1994, of record) has been fully considered.

Amended claims 1 and 16 require a liquid preparation comprising 1 w/w% to 20 w/w% of a camptothecin derivative. However, Harada et al. discloses the compound T-0128 in saline at 0.5 mg/ml of T-2513, or 7-ethyl-10-aminopropyloxy-camptothecin (page 403, left column, lines 22-23). T-2153 has a molecular weight of approximately 485 g/mol. The compound T-0128 has a molecular weight of approximately 130,000 g/mol (page 402, lines 21-23). Therefore a liquid saline preparation that contains T-0128 at an amount equal to 0.5 mg/mL of T-2513 contains approximately 13.4 w/w% of the camptothecin derivative as calculated below:

(0.5 mg T-2153/mL H_2O * 130,000 g/mol T-0128 / 485 g/mol T-2153)

$\approx$ 134 mg T-0128/mL H_2O / 1000 mg/mL $H_2O \approx$ 134 mg T-0128 / 1000 mg H_2O

Therefore Harada et al. as relied upon in the Office Action mailed 23 Aug 2007 discloses a liquid preparation comprising approximately 13.4 w/w% of the camptothecin derivative, addressing the range of instant claims 1 and 16 as amended.

Conclusion

No claim is found to be allowable.

Applicant's amendment necessitated the new or modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

2/1/08

Jonathan S. Lau
Patent Examiner
Art Unit 1623

Shaojia Anna Jiang, Ph.D.
Supervisory Patent Examiner
Art Unit 1623